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EXAMINER	
SAKELARIS, SALLY A	

ART UNIT	PAPER NUMBER
1634	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/904,968	GERMINO ET AL.	
	Examiner	Art Unit	
	Sally A Sakelaris	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 June 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-75* is/are pending in the application.

4a) Of the above claim(s) *18,30,58 and 67* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-17 19-29 31-57 59-66 and 68-75* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: SEQALIGNMENTS (4 pgs)

DETAILED ACTION

This action is written in response to applicant's correspondence submitted 6/1/2004. Claims 1, 2, 5, 7, 12, 20, 63, 65, and 66 have been amended, no claims have been canceled, and no claims have been added. Claims 1-75 are pending while claims 18, 30, 58, and 67 have been withdrawn. Applicant's amendments and arguments have been thoroughly reviewed, but are not persuasive for the reasons that follow. Any rejections not reiterated in this action have been withdrawn as necessitated by applicant's amendments to the claims. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. **This action is non-FINAL.**

Response to Arguments

Applicant's arguments, see pages 1-45, filed 6/1/2004, with respect to the rejection(s)of claim(s) 1-7, 20-22, 25, 31, 37-39, 43-44, 46-49, 59, 62 under 102(b), Claims 16-17, 19, 40 and 42 under 102(b), and claim 41 under 103(a) have been fully considered and are persuasive. Therefore, the rejection has been withdrawn. However, upon further consideration, new ground(s) of rejection have been made in view of Klinger and in further view of Stefano, Buck et al., Shapira et al., Sathe et al., Iliff et al., Ahern et al., and Koster et al. and combinations thereof(Please see new rejections below). It should also be noted that in response to applicant's arguments that no sequence alignments were provided with the previous rejection, the alignments were provided(see PTO-326) but were not sent to applicant evidently. Applicant can now access the document in public/private pair on the internet, it is the 14 page document from 2/03/2003 labeled as examiner search notes. It is again included in this action though as a

courtesy. As such, applicant's arguments with respect to the previous rejections have been considered but are moot in view of the new ground(s) of rejection.

Claim Interpretations

It should be noted that the claim language including "selectively hybridize" is interpreted as being able to hybridize under any sort of stringency conditions.

Also, recitations of "about", "about 50" etc. will be interpreted liberally as an exact definition of these terms in the specification could not be located.

Response to Arguments:

With respect to the claim language "selectively hybridize", applicants "submit that this interpretation would not appear to be reasonable to the extent that the 'any sort of stringency conditions' contemplated by the examiner would not result in 'selective hybridization'" (Applicant's response page 25). Their given description reference points out only that the term refers to "the ability of an oligonucleotide probe to hybridize to a selected sequence, but not to a highly related nucleotide sequence". This disclosure provides only an exemplary definition and as such will not be read into the claims as a limitation. In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e. structural limitations of a DNA sequence that is able to "selectively hybridize") is not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Lastly, with respect to the claims' recitation of the term "about" and "about 50", while applicant's disclosure of "an example of the meaning of the term 'about' is provided with respect to primers as including one or few additional, or lacking one or few, nucleotides at one or both ends of a primer". The example does not provide an explicit definition by which the term may be defined. As such the term was interpreted to its broadest.

THE FOLLOWING ARE NEW GROUNDS OF REJECTION NECESSITATED BY APPLICANT'S ARGUMENTS

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

1. Claims 1-7, 20-22, 25, 31, 37-39, 43-44, 46-49, 59, and 62 are rejected under 35 U.S.C. 103(a) as being unpatentable over Klinger et al.(US Patent 5,654,170).

With regard to claim 1, Klinger et al. teach a primer comprising a 5' region and adjacent 3' region, said region comprising a nucleotide sequence that selectively hybridizes to a PKD1 gene sequence and, optionally, to a PKD1 gene homolog sequence, and said 3' region

comprising a nucleotide sequence that selectively hybridizes to a PKD1 gene sequence, and not to a PKD1 gene homolog sequence, provided the primer does not consist of a sequence as set forth in SEQ ID NO:11, 18, 52, and 60(Abstract, Col. 5 lines 45-67 – Col. 6 1-4 and figure 3B).

With regard to claims 2-4, Klinger teaches the above primer wherein said 5'region comprises at least about ten contiguous nucleotides, wherein the 3'region comprises at least one 3'terminal nucleotide identical to a nucleotide that is 5' and adjacent to the nucleotide sequence of the PKD1 gene to which the 5' region of the primer can hybridize, and wherein said 3' terminal nucleotide is different from a nucleotide that is 5' and adjacent to a nucleotide sequence of the PKD1 homolog to which the 5' region of the primer can hybridize wherein the 3' region comprises about 2 to 4 3' terminal nucleotides and a 5' region of about 14 to 18 nucleotides and a 3' region of about 2 to 6 nucleotides in their teaching of the primer in Figure 3B of 5'AGGACCTGTCCAGGCATC 3'.

With regard to claims 5-7, Klinger teaches in Col. 5, that the "present invention encompasses isolated oligonucleotides corresponding to sequences within the PKD1 gene and PKD1cDNA, which, alone or together, can be used to discriminate between the authentic expressed PKD1 gene and PKD1 homologues or other repeated sequences. These oligonucleotides may be from about 12 to about 60 nucleotides in length, preferably about 18 nucleotides; may be single or double stranded, and may be labeled or modified as described below. An example of an oligonucleotide that can be used in this manner is shown in Fig. 3B"(Col. 5). (Note: art has been applied according to the specification's definition of "substantially identical" on page 21, a primer with "at least about 80% identity to one of SEQ ID NOS: 3 to 51 and 61 to 113")

With regard to claim 20, 59, and 62, Klinger et al. teach an isolated polynucleotide, comprising a contiguous sequence of at least about ten nucleotides substantially identical to a nucleotide sequence of SEQ ID NO:1 or to a nucleotide sequence complementary thereto, the contiguous nucleotide sequence comprising a position corresponding to nucleotide 3336, wherein nucleotide 3336 is deleted(Col. 5 lines 45-67 and Col. 6 lines1-17). Furthermore, the reference teaches that "deletions may be detected using a PCR-based assay , in which pairs of oligonucleotides are used to prime amplification reactions and the sizes of the amplification products are compared with those of control products"(Col. 8 lines 36-40).

With regard to claims 21 and 22, Klinger et al. teach the above polynucleotides in a vector and furthermore the host cell transformed by this vector. The abstract teaches that "the invention also encompasses vectors comprising these nucleic acids, host cells transformed with the vectors"(+ Col. 6 lines 39-67 and Col. 7 lines 1-15).

With regard to claim 25 and 43, Klinger et al. teach a method of detecting the presence or absence of a mutation in a PKD1 polynucleotide in a sample, the method comprising: contacting nucleic acid molecules in a sample with at least one primer pair of claim 7 under conditions suitable for amplification of a PKD1 polynucleotide by the primer pair, thereby generating a PKD1-specific amplification product, under said conditions; and identifying the presence or absence of a mutation in the PKD1-specific amplification product, thereby detecting the presence or absence of a mutation in the PKD1 polynucleotide in the sample(See for example Col. 8 lines 35-60 and Col. 9 lines 47-67 and Col. 10 lines 1-40).

With regard to claim 31, Klinger et al. further teach the above method of identifying the presence or absence of a mutation in the amplification product comprises determining the

nucleotide sequence of the amplification product as taught in the embodiment of the assay used to detect the presence of mutation in Col. 10 for example of "direct DNA sequencing" line 35(+ Col. 8 lines 35-38).

With regard to claim 37, 44 and 49 Klinger et al. teach the method of detecting a presence or the absence of a mutation wherein a primer extension assay is used and performed with a detectably labeled primer(Col. 5 line 52) and a mixture of deoxynucleotides and dideoxynucleotides(sequencing and also see Col. 14 lines 1-10), and wherein the primer are selected so as to enable differential extension of the primer in the presence of a wild-type PKD1 polynucleotide as compared to a mutant PKD1 polynucleotide. Although the sequencing method taught by the reference(Col. 10 line 35) teaches the limitation of claim 37, the PCR reaction of Cols 13 and 14 also anticipate the limitation of 37 and 44 in their use of a sample from a subject("whole blood samples" Col. 12 line 63) to obtain their data.

With regard to claims 38, 39, and 48 Klinger teaches that the above method is performed both using a plurality of primer pairs and in a high throughput format utilizing a plurality of samples(Col. 11, lines 11-17).

With regard to claims 46-47 wherein identifying the presence or absence of a mutation in the amplification product is associated with the PKD1-associated disorder autosomal dominant polycystic kidney disease(Col. 1 lines 10-49).

Klinger et al. does not teach in Figure 3, a primer that is extendable on its 3' because of a polymerization blocking agent.

However, Klinger et al. do teach both the authentic PKD1 sequence, the homolog PKD1 sequence, and primers to amplify both of these and to amplify preferentially the authentic

sequence alone. Furthermore, the reference in Column 8 lines 46-60 teaches that a "confounding and complicating factor in the detection of a PKD1 mutation is the presence of PKD1 homologues at several sites on chromosome 16" and that in "analysis of mutations in PKD1, it is critical to distinguish between sequences derived from any of the homologues".

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have practiced the teachings of Klinger et al. to have obtained a primer as claimed capable of differentiating between the authentic and homolog PKD1 sequence for their provided expected benefit that "an important feature of the present invention is the provision of oligonucleotide primers that discriminate between authentic PKD1 and the homolgues"(Col. 8 line 53-55). The reference goes on to teach that "a detailed comparison of the sequences of the authentic PKD1 gene and the homologues enables design of primers that discriminate between the authentic PKD1 gene or cDNA and the homologues"(Col. 8 line 55-60). Thus, in light of these teachings of the desirability of making primers that are able to discriminate between the PKD1 gene sequence and the PKD1 homolog, it would have been obvious for one of ordinary skill in the art at the time the invention was made to have used the sequence of Figure 3A to make primers with a free 3' hydroxyl group through which subsequent extension of a non-homolog sequence could be achieved during an amplification reaction.

2. Claims 16-17, 19, 40-42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Klinger et al.(US Patent 5,654,170) in view of Stefano(US Patent 6,297,010).

While the teachings of Klinger et al. can be read above, the reference does not teach the limitation of claims 16-19 and 40 and 42 that include the primers immobilization on a solid matrix such as a microchip or an array.

However, Stefano teaches high density arrays of bound nucleotides used in methods for "high-throughput analysis of DNA, i.e., the rapid and simultaneous analysis of DNA, i.e., the rapid and simultaneous processing of DNA samples derived from a large number of patients"(Column 16 lines 57-65). The reference teaches a "method for identification of one or more mutation(s) in a sample polynucleotide by immobilizing a plurality of sample polynucleotides on a single solid support"(Col. 4 lines 40-44). The reference further provides that the solid support may be matrices such as "treated or untreated microtiter plates" or in the case of "amino-modified PCR products can be bound to silylated glass surfaces"(Col. 12 lines 11-45).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have combined the teachings of Klinger's method and primers and practiced them on the solid support of Stefano since the "cost and labor required to sequence every patient DNA sample over these important regions would make the detection of pathogenic mutations extremely slow and prohibitively expensive"(Col. 3 lines 9-20) and for the expected benefit that their method provides that "both indicates the presence of unknown mutations and which directly provides the sequence alterations"(Col. 3) through their high-throughput analysis of DNA.

3. Claims 8-15, 26, 28, 29, 54, 68-72, and 74 are rejected under 35 U.S.C. 103(a) as being unpatentable over Klinger et al.(US Patent 5,654,170) in view of Buck et al (Biotechniques (1999) 27(3):528-536).

While the teachings of Klinger et al. can be read above, with regard to Claims 8-15, 26, 28, 29, 54, 68-72, and 74, Klinger et al. teach SEQ ID NO:1, which includes all of the SEQ ID NOS of 3, 4, 19 and 20(See attached alignments). While Klinger et al. define their 31,571 base pair sequence as the PKD1 genomic sequence and furthermore teach the "isolated oligonucleotides corresponding to sequences within the PKD1 gene or within the PKD1 cDNA, which alone or together, can be used to discriminate between the authentic expressed PKD1 gene and PKD1 homologues or other repeated sequences"(Col. 5, lines 40-55) and also "an example of an oligonucleotide that can be used in this manner(See Fig. 3B); Klinger does not teach the primer sequences of SEQ ID NOS of 3, 4, 19 and 20, only the sequences in the genomic form of their SEQ ID NO:1(see alignments).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have selected the primers of SEQ ID NOS: 3, 4, 19 and 20 from the Klinger's known sequence of SEQ ID NO: 1 for the expected benefit of obtaining functionally equivalent primers with the ability to "selectively prevent the amplification of PKD1 homologue sequences. In this manner authentic PKD1 sequences are selectively amplified"(Col. 5 lines 64-67)

In the recent court decision *In Re Deuel* 34 USPQ 2d 1210 (Fed. Cir. 1995), the Court of Appeals for the Federal Circuit determined that the existence of a general method of identifying

a specific DNA does not make the specific DNA obvious. Regarding structural or functional homologs, however, the Court stated,

"Normally, a *prima facie* case of obviousness is based upon structural similiarity, i.e., an established structural relationship between a prior art compound and the claimed compound. Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologs because homologs often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties (see page 9, paragraph 4 of attached ref)."

Since the claimed primers simply represent structural homologs, which are derived from sequences suggested by the prior art as useful for primers and probes for the detection of PDK1, and in particular for the detection of the authentic sequence of PDK1 not homologs, and concerning which a biochemist of ordinary skill would attempt to obtain alternate compounds with improved properties, the claimed primers and probes are *prima facie* obvious over the cited references in the absence of secondary considerations.

Buck expressly provides evidence of the equivalence of primers. Specifically, Buck invited primer submissions from a number of labs (39) (page 532, column 3), with 69 different primers being submitted (see page 530, column 1). Buck also tested 95 primers spaced at 3 nucleotide intervals along the entire sequence at issue, thereby testing more than 1/3 of all possible 18 mer primers on the 300 base pair sequence (see page 530, column 1). When Buck tested each of the primers selected by the methods of the different labs, Buck found that EVERY SINGLE PRIMER worked (see page 533, column 1). Only one primer ever failed, No. 8, and that primer functioned when repeated. Further, EVERY SINGLE CONTROL PRIMER functioned as well (see page 533, column 1). Buck expressly states "The results of the empirical sequencing analysis were surprising in that nearly all of the primers yielded data of extremely high quality (page 535, column 2)." Therefore, Buck provides direct evidence that all primers would be expected to function, and in particular, all primers selected according to the ordinary criteria, however different, used by 39 different laboratories. It is particularly striking that all 95

control primers functioned, which represent 1/3 of all possible primers in the target region. This clearly shows that every primer would have a reasonable expectation of success.

4. Claims 27, 53, 55, 60, 61, 73, and 75 are rejected under 35 U.S.C. 103(a) as being unpatentable over Klinger et al.(US Patent 5,654,170) in view of Buck et al (Biotechniques (1999) 27(3):528-536) and further in view of Shapira et al.(PNAS 1991)

While the teachings of Klinger et al. in view of Buck et al. can be read above, the two references do not teach the limitation of claims 27, 53, 55, 60, 61, 73, and 75 that includes the nesting of primer pairs one inside the other.

However, Shapira et al. teach a method of amplifying nucleic acids by way of nested primer pairs. The reference teaches that following a first round of PCR, "a second round of PCR utilizing the nested primers in Fig. 2 in a reaction mixture containing the same concentrations of all of the above constituents, except for 1.5 mM MgCl2 and a 5ul aliquot of the previous PCR reaction mixture that served as the DNA template"(Pg. 7529 left).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have combined the nesting of primer pairs teachings of Shapira with nested the SEQ ID NOS: 3, 4, 19 and 20 as taught by Klinger et al in view of Buck for the expected benefit that "nested-primer PCR provided the sensitivity to analyze…that was not available with Southern blotting techniques"(Pg. 7528 right).

5. Claims 32-33 and 35-36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Klinger et al.(US Patent 5,654,170) in view of Buck et al (Biotechniques (1999) 27(3):528-536) and further in view of Sathe et al.(US Patent 6,362,326).

While the teachings of Klinger et al. in view of Buck et al. can be read above, the two references do not teach the limitation of claims 32-33 and 35-36 that include the use of temperature melting, HPLC, and SSCP analysis on the amplification products in order to identify the presence or absence of a mutation.

However, Sathe et al. teach the detection of mutations on the DNA level through "single-stranded conformation polymorphism assay (SSCA or SSCP)"(Col. 8 lines64-65). The references continues to teach that the "increased throughput possible with SSCA makes it an attractive, viable alternative to direct sequencing for mutation detection"(Col. 9 lines 1-10). Even further, "denaturing HPLC, similar to SSCP, can be used which uses a PCR amplified product, run down a heated HPLC column; the heating disassociates the DNA strands and one usually sees two peaks if there is a variation in allelic forms"(Col. 9 lines 14-18) "and it works on the same principles as SSCP"

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have combined the teachings of Sathe's SSCA and HPLC in mutation detection to method and SEQ ID NOS: 3, 4, 19 and 20 as taught by Klinger et al in view of Buck for the expected benefit of these techniques being a "viable alternative to direct sequencing for mutation detection"(Col. 9 lines 1-10).

6. Claims 50-52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Klinger et al.(US Patent 5,654,170) in view of Iliff (US Patent 6,234,964).

While the teachings of Klinger can be seen above, the reference does not teach the limitations of claims 50-52 including transmitting a report to a user via internet, fax or mail.

However, Iliff teach a disease management system that "gives the patient the option of receiving a summary of the consultation session and specific recommendations provided by the system via facsimile, electronic mail, or mail service"(Col. 12 lines30-67).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have combined the teachings of Klinger's method and primer and transmitted their resulting data through a report to a user using a fax, e-mail, or regular mail of Iliff for the expected benefit of "promoting patient health in an automated manner that reduces costly medical intervention"(Abstract).

7. Claims 55-57 are rejected under 35 U.S.C. 103(a) as being unpatentable over Klinger et al.(US Patent 5,654,170) in view of Buck et al (Biotechniques (1999) 27(3):528-536) and further in view of Shapira et al.(PNAS 1991) in further view of Sathe et al.(US Patent 6,362,326).

While the teachings of Klinger et al. in view of Buck et al. and in a further view of Shapira et al. can be read above, but the three references do not teach the limitation of claims 55-57 of temperature melting, HPLC, and SSCP analysis on the amplification products in order to identify the presence or absence of a mutation.

However, Sathe et al. teach the detection of mutations on the DNA level through "single-stranded conformation polymorphism assay (SSCA or SSCP)"(Col. 8 lines64-65). The

references continues to teach that the "increased throughput possible with SSCA makes it an attractive, viable alternative to direct sequencing for mutation detection"(Col. 9 lines 1-10). Even further, "denaturing HPLC, similar to SSCP, can be used which uses a PCR amplified product, run down a heated HPLC column; the heating disassociates the DNA strands and one usually sees two peaks if there is a variation in allelic forms"(Col. 9 lines 14-18) "and it works on the same principles as SSCP"

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have combined the teachings of Sathe's SSCA and HPLC in mutation detection to the nested primer pair method and SEQ ID NOS: 3, 4, 19 and 20 as taught by Klinger et al in view of Buck and in further view of Shapira for the expected benefit of these techniques being a "viable alternative to direct sequencing for mutation detection"(Col. 9 lines 1-10).

8. Claims 63-66 are rejected under 35 U.S.C. 103(a) as being unpatentable over Klinger et al.(US Patent 5,654,170) in view of Ahern et al.(The Scientist, 1995)

While the teachings of Klinger et al are summarized above, the reference does not teach a kit for detecting the presence or absence of a mutation in a PKD1 gene,

However, Ahern teaches that "biochemical, reagents kits offer scientists good return on inventment" as combining the reagents into a kit form offers scientists "the opportunity to better manage their time, putting these products all together in kits takes the convenience one step further"(Pg. 4 top).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have combined the teachings of Klinger's primers and methods into a kit taught by Ahern for the expected benefit of "buying premade reagents and kits because they are convenient and they save time"(Pg. 4).

9. Claim 34 is rejected under 35 U.S.C. 103(a) as being unpatentable over Klinger et al.(US Patent 5,654,170) in view of Buck et al (Biotechniques (1999) 27(3):528-536) and further in view of Koster et al.(US Patent 6,225,450).

While the teachings of Klinger et al. in view of Buck et al. can be read above, the two references do not teach the limitation of claim 34 that includes the use of matrix-assisted laser desorption time of flight mass spectrometry on the amplification products in order to identify the presence or absence of a mutation.

However, Koster et al. teach a method of "DNA sequencing that utilizes the sanger sequencing strategy and assembles the sequence information by analysis of the nested fragments obtained by base-specific chain termination via their different molecular masses using mass spectrometry as for example Maldi(Abstract)" The reference further teaches that "MALDI can

be particularly attractive when a time of flight (TOF) configuration is used as a mass analyzer"(Col. 6 lines 45-47).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have combined the teachings of Koster's MALDI TOF method and SEQ ID NOS: 3, 4, 19 and 20 as taught by Klinger et al in view of Buck for the expected benefit of these techniques providing a "high speed, high throughput, no electrophoresis and gel reading artifacts…and no costly reagents involving various substitutions with stable isotopes"(Abstract).

35 U.S.C. 112, Written Description Rejection

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 1-17, 19-29, 31-57, 59-66 and 68-75 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention

The specification discloses SEQ ID NO: 1 which the specification asserts corresponds to the wt PKD1 gene(pg. 26). Claims 1-66 and 68-75 are directed to encompass sequences comprising nucleotides that selectively hybridize to a PKD1 gene sequence and optionally to a PKD1 homolog sequence, primers comprising regions wherein at least 10 contiguous nucleotides that "can hybridize", primers comprising regions which "can selectively hybridize to a nucleotide sequence flanking and within about fifty nucleotides", primers comprising a nucleotide sequence substantially identical to any of SEQ ID NOS 3, 4, 19, or 20, primers which

can amplify a portion of SEQ ID NO:1 comprising about nucleotides 2043 to 4209, etc. For example, claim 7 as written could encompass any T3 and T7 primer pair that "can amplify" a cloned region of SEQ ID NO:1 comprising about nt 2043 to 4209. Thus, the instant claims encompass nucleic acids and methods that comprise any number of potential sequences when one considers that they encompass nucleic acids that comprise partial matches to the recited SEQ ID numbers and the ability to "hybridize" to and "can amplify" even more sequences. This genus can read on any number of possible primers comprising any number of known and unkown nucleic acid fragments, yet the specification has only disclosed the nucleic acids of SEQ ID NO: 1 and primers of SEQ ID NOS: 3, 4, 19, and 20. A review of the full content of the specification indicates that the sequence of nucleotides of SEQ ID NO: 1 and all aforementioned variations, are essential to the operation and function of the claimed invention. None of these sequences meet the written description provision of 35 USC 112, first paragraph. The specification provides insufficient written description to support the genus encompassed by the claim.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

With the exception of SEQ ID NO: 1, 3, 4, 19 and 20, the skilled artisan cannot envision the detailed chemical structure of the encompassed polynucleotides regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The nucleic acid itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. In Fiddes v. Baird, 30 USPQ2d 1481, 1483, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence.

Finally, University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404, 1405 held that:

> ...To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); *In re Gosteli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (" [T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." *Lockwood*, 107 F.3d at 1572, 41 USPQ2d at 1966.
>
> An adequate written description of a DNA, such as the cDNA of the recombinant plasmids and microorganisms of the '525 patent, "requires a precise definition, such as by structure, formula, chemical name, or physical properties," not a mere wish or plan for obtaining the claimed chemical invention. *Fiers v. Revel*, 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993). Accordingly, "an adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself." Id. at 1170, 25 USPQ2d at 1606.
>
> The named ORF is not itself a written description of that DNA; it conveys no distinguishing information concerning its identity. While the example provides a process for isolating and characterizing cDNA sequences from *E. grandis*, there is no further information in the patent pertaining to that cDNA's relevant structural or physical characteristics; in other words, it thus does not describe *E. grandis* cDNA. Describing a method of preparing a cDNA or even describing the protein that the cDNA encodes, as the specification does, does not necessarily describe the cDNA itself. No sequence information indicating which nucleotides constitute *E. grandis* cDNA appears in the application. Accordingly, the specification does not provide a written description of the invention of claims 1, 4, and 6-15.

Therefore, none of the sequences encompassed by the claim meets the written description provision of 35 USC 112, first paragraph. The species specifically disclosed are not representative of the genus because the genus is highly variant. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. (See page 1115.)

Any inquiry concerning this communication or earlier communication from the examiner should be directed to Sally Sakelaris whose telephone number is (571)272-0748. The examiner

can normally be reached on Monday-Thursday from 7:30AM-5:00PM and Friday from 1:00PM-5:00PM.

If attempts to reach the examiner are unsuccessful, the primary examiner in charge of the prosecution of this case, Jeffrey Fredman, can be reached at (571)272-0742. If attempts to reach the examiners are unsuccessful, the examiner's supervisor, Gary Benzion, can be reached on (571)272-0782. The official fax number is (703)872-9306.

Any inquiry of a general nature or relating to the status of this application should be directed to Chantae Dessau whose telephone number is (571)272-0518.

Sally Sakelaris

8/18/2004

JEFFREY FREDMAN
PRIMARY EXAMINER
8.18.04